Citation:

Streppel MT, Ocké MC, Boshuizen HC, Kok FJ, Kromhout D. Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen study. *Eur Heart J*. 2008 Aug;29(16):2024-30. Epub 2008 Jul 18.

PubMed ID: 18641046

Study Design:

Longitudinal Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess the relationship between fish consumption or eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) intake from fish, and sudden coronary death.

Inclusion Criteria:

- Participants from the Zutphen Study, a cohort of men born between 1900 and 1920 and examined repeatedly between 1960 and 2000

Exclusion Criteria:

None specifically mentioned.

Description of Study Protocol:

Recruitment

- Participants from the Zutphen Study, which started as the Dutch contribution to the Seven Countries Study, a longitudinal study of the relationships between diet, other risk factors, and chronic diseases.
- In 1960, a random sample of 1,088 men born between 1900 and 1919 and residing in Zutphen for at least 5 years was drawn
- Of those men, 878 participated in the Zutphen Study and 872 took part in both dietary and physical examinations, which were repeated in 1965 and 1970
- In 1985, the 554 survivors was extended with a new random sample of men of the same birth cohort
- Of the 1266 men who were invited, 939 men participated and 825 men took part in both dietary and physical examinations, which were repeated in 1990, 1995 and 2000

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Design: Longitudinal cohort study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Hazard ratios were obtained from time-dependent Cox regression models
- For missing observations, the nearest value was imputed
- Participants were divided into consumers and non-consumers of total fish, fatty fish and lean fish according to their recent and long-term (cumulative average) fish consumption
- Participants were also grouped into three groups according to recent and long-term intake of EPA + DHA from fish: 0, 0 - 250 and >250 mg.
- P-values for trends were calculated using the continuously distributed variable

Data Collection Summary:

Timing of Measurements

- Men were examined repeatedly between 1960 and 2000
- Up to 7 repeated measures of fish consumption and EPA + DHA intake from fish were collected over 40 years of follow-up

Dependent Variables

- Sudden coronary heart disease death
- Final causes of death were ascertained by one clinical epidemiologist and coded according to the Eight Revision of the International Classification of Diseases
- CHD deaths were coded 410-414, including cases of sudden death

Independent Variables

- Fish consumption and n-3 fatty acid intake
- Information on habitual food consumption was collected by using the cross-check dietary history method
- Total fish consumption was divided into fatty (salmon, mackerel, herring, eel and sardines) and lean (codfish, plaice and pollock) fish
- Daily EPA + DHA intake was calculated using Dutch food composition tables

Control Variables

- Total energy intake
- Alcohol intake
- Wine use
- Fruit and vegetable consumption
- Saturated fat
- *Trans* unsaturated fatty acid, *cis* monounsaturated fat and *cis* polyunsaturated fat intake
- Use of a serum cholesterol lowering diet
- Cigar or pipe smoking
- Cigarette smoking duration
- BMI

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- Prevalence of diabetes mellitus
- Systolic blood pressure
- Baseline socioeconomic status

Description of Actual Data Sample:

Initial N:

- From original cohort, 872 took part in both dietary and physical examinations, which were repeated in 1965 and 1970
- In 1985, the 554 survivors was extended with a new random sample of men of the same birth cohort
- Of the 1266 men who were invited, 939 men participated and 825 men took part in both dietary and physical examinations, which were repeated in 1990, 1995 and 2000

Attrition (final N): 1373 men were included in the analysis

Age: born between 1900 and 1920, mean survival age: 77 years

Ethnicity: not mentioned

Other relevant demographics:

Anthropometrics

Location: The Netherlands

Summary of Results:

Key Findings

- During 40 years of follow-up, 348 of the 1373 men died from CHD; of these deaths, 66 were sudden coronary deaths (19% of all CHD deaths)
- Among the men included in the study in 1960, the percentage of fish consumers varied between 71% and 81% between 1960 and 2000 and average fish consumption ranged from 16 to 21 grams per day
- Lean fish was the major type of fish consumed (58% - 80% of total fish consumption)
- Average EPA + DHA intake from fish varied between 136 and 236 mg per day in the period 1960 - 2000
- Among the men included in the study in 1985, fish consumption and EPA + DHA intake from fish was comparable with the men participating since 1960
- Long-term fish consumers, consuming on average 22 g per day, had a 27% lower CHD death risk (P = 0.16) while recent fish consumption was not associated with CHD death.
- Long-term fish consumption was inversely associated (borderline significant) with coronary heart disease (CHD) death, however, the strength of the association decreased from age 50 (hazard ratio = 0.32, 95% confidence interval: 0.13 - 0.80) until age 80 (hazard ratio = 1.34, 95% confidence interval: 0.58 - 3.12).
- For men with a daily EPA + DHA intake from fish below 250 mg compared with no intake, CHD death risk was reduced to the same extent as for men with a daily intake above 250 mg (P for trend = 0.27).

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- Long-term fatty-fish consumption, on average 7 g per day, lowered sudden coronary death risk by 54%, while no associations were found with total and lean fish consumption.
- Long-term fatty-fish consumption lowered the risk of sudden coronary death (hazard ratio = 0.46, 95% confidence interval: 0.27 - 0.78).

Author Conclusion:

The main conclusion of this study is that long-term fish consumption, on average 22 g per day, lowers the risk of CHD death, especially below age 65. Fatty-fish consumption lowers the risk of sudden coronary death. There is no clear dose-response relationship between EPA + DHA intake from fish and sudden coronary death.

Reviewer Comments:

Up to 7 repeated measures of fish consumption and EPA + DHA intake from fish were collected over 40 years of follow-up, but not all participants were part of the cohort during that time period. Authors note the following limitations:

- *Number of sudden coronary deaths (66 events) observed in the Zutphen Study may have been too small to detect a dose-response relation for EPA + DHA intake*
- *To account for changes in product composition, time-specific food composition tables are needed to calculated nutrient intake over a longer period of time*
- *It was not possible to consider different methods of fish preparation*
- *For men who were newly included in the study in 1985, information on fish consumption was missing in the period 1960-1970*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes

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1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	???
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes

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4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	No
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes

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7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	???
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes

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